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Power washing pulmonary alveolar proteinosis

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ABSTRACT

Pulmonary alveolar proteinosis is an uncommon cause of insidious onset shortness of breath and hypoxemia. It is caused by an accumulation of surfactant within the alveoli. Left untreated, it can be fatal. Standard-of-care treatment is whole-lung lavage; however, in severe cases, the associated hypoxemia can be profound and single-lung ventilation would not be tolerated, potentially preventing a lifesaving treatment. Single cases using veno-venous extracorporeal membrane oxygenation to perform whole-lung lavage have been reported. Here we describe three patients with severe pulmonary alveolar proteinosis who were successfully treated with whole-lung lavage using veno-venous extracorporeal membrane oxygenation for oxygenation support.

KEYWORDS Crazy paving; ECMO; PAP; pulmonary alveolar proteinosis; whole-lung lavage

Pulmonary alveolar proteinosis (PAP) is a rare source of dyspnea caused by alveolar lipoprotein accumulation.[1,2] Imaging demonstrates interstitial thickening with ground glass infiltrates called "crazy paving" but is not pathognomonic. Alveoli fill with lipoprotein-rich material positive for periodic acid–Schiff on staining.[3] Whole-lung lavage (WLL) is the standard of care; it ventilates one lung while the other is lavaged with large volume fluids to disimpact accumulated alveolar surfactant with the goal of improving oxygenation.[4] Traditionally, lavage of each lung can be done separately. However, severely hypoxemic patients are precluded from lavaging even one lung.[5] Veno-venous extracorporeal membrane oxygenation (VV-ECMO) has emerged as a means to provide oxygenation during WLL.[6–8] We present our experience using VV-ECMO for WLL in three severely hypoxemic patients with PAP.

CASE DESCRIPTIONS

Briefly, patient 1 is a 53-year-old man with 12 months of progressive dyspnea with tobacco and sandblasting exposures. Patient 2 is a 47-year-old man with 15 months of dyspnea with tobacco, sandblasting, heavy metal, and noxious fumes exposures. Patient 3 is a 44-year-old man with 1 month of progressive dyspnea and tobacco exposure but no other exposures. They all demonstrated "crazy paving" on computed tomography (CT) and positive periodic acid–Schiff staining on pathology *(Figure 1)*. Descriptions of the patients' demographic characteristics, presentations, and clinical courses are outlined in *Table 1*.

DISCUSSION

PAP is an orphan disease causing dyspnea, pulmonary infiltrates, and hypoxia with an insidious onset, potentially delaying diagnosis and severity at presentation. PAP is closely associated with an autoantibody to granulocyte-macrophage colony-stimulating factor (GM-CSF), with up to 95% of cases demonstrating GM-CSF antibodies.[1] GM-CSF is produced by type II alveolar cells and is required for macrophage maturation. The pathogenesis of PAP centers on the absence of GM-CSF and mature macrophages, causing accumulation of surfactant within the alveoli, which impairs oxygenation and ventilation and leads to macrophage dysfunction.[9]

The patients in this series demonstrated classical risk factors for PAP, including male gender, active smoking, and occupational exposures (sandblasting).[10,11] Opportunistic

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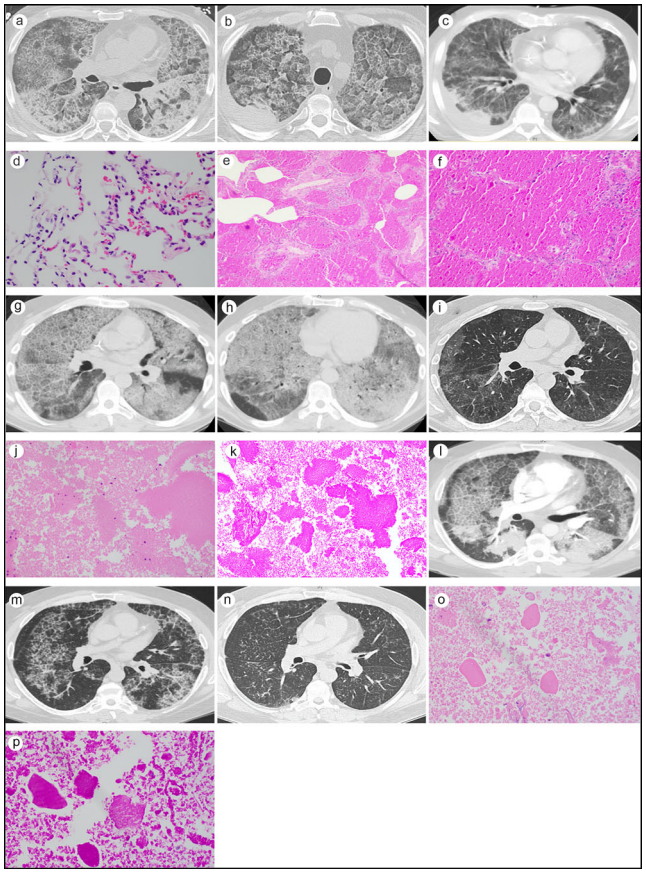

Figure 1. Figure 1. **(a-f)** Patient 1. **(a, b)** High-resolution CT images before whole-lung lavage. **(c)** Noncontrast CT image 4 days after whole-lung lavage. **(d)** Representative pathology slide of normal lung biopsy using hematoxylin and eosin (H&E) stain. **(e)** Video-assisted thoracoscopic surgery biopsy -attained pathology slide using H&E stain demonstrating alveoli full of amorphous, granular eosinophilic material. **(f)** Pathology slide using periodic acid -Schiff staining with very strongly pink staining and considerable amounts of granular material. **(g-k)** Patient 2. **(g, h)** Noncontrast CT images before whole-lung lavage. **(i)** High-resolution CT image after whole-lung lavage. **(j)** Bronchoalveolar lavage (BAL) -obtained pathology slide using H&E stain demonstrating amorphous, granular eosinophilic material. **(k)** BAL-obtained pathology slide using periodic acid -Schiff staining with strong positive staining. **(l-p)** Patient 3. **(l)** CT angiogram image before whole-lung lavage. **(m)** Noncontrast CT image 6 months after whole-lung lavage. **(n)** Noncontrast CT following repeat whole-lung lavage. **(o)** BAL-obtained pathology slide using H&E stain demonstrating amorphous, granular eosinophilic material. **(p)** BAL-obtained pathology slide using periodic acid -Schiff staining with strong positive staining.

infections are commonly observed in PAP.[10,12] Patients 1 and 3 grew *Mycobacterium avium* complex (MAC) from cultures of the WLL and patient 2 was previously treated for MAC from prior bronchoscopy, demonstrating that it can precede or follow the diagnosis of PAP.[12] *Nocardia* spp. have also been linked to PAP.[12] Patient 2 was previously empirically treated for *Nocardia*.

Treatment guidelines recommend WLL using a dual-lumen endotracheal tube for alveolar clearance. Sequential single-lung lavage is preferred in the literature and in our institution; however, those with severe presentations of PAP cannot tolerate single-lung ventilation. Other oxygenation approaches have been attempted, including hyperbaric lavage and nonventilated lung pulmonary artery occlusion to control shunting, but VV-ECMO has emerged as the primary support therapy to facilitate WLL in the most severe disease.[6–8,13]

Due to the slow onset of PAP, severe presentations rarely occur. As a result, WLL using ECMO support has been reported as individual cases. Here, we report three cases of initial presentations of severe PAP with severe hypoxia that required VV-ECMO support for WLL. All of the patients were decannulated from ECMO within 48 hours with significant improvement in oxygenation post-lavage. VV-ECMO for WLL should be reserved for the most severe cases with sequential single-lung lavage used preferentially. However, in those patients with severe hypoxemia, intolerant of single-lung ventilation, our experience is that VV-ECMO is a viable means to support oxygenation during WLL.

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Table 1. Characteristics of three patients with severe pulmonary alveolar proteinosis who required veno-venous extracorporeal membrane oxygenation support for whole-lung lavage

Category	Variable	Patient 1	Patient 2	Patient 3
Demographic characteristics	Age	53	47	44
	Gender	Male	Male	Male
	Smoking years	44	40	>20
	Exposures	Sandblasting	Fumes, heavy metals, sandblasting	None
	Medical history	HTN, OA	COPD, MAC, nocardiosis	DM, OSA
Presentation	Symptoms	Dyspnea	Dyspnea, weight loss, anorexia	Dyspnea, fatigue
	Duration (months)	12	15	1
	Previous evaluation	ED	Pulmonologist	ED
	Previous treatments	Antibiotics	Antibiotics	Antibiotics
Diagnostics	"Crazy paving" on CT	Yes	Yes	Yes
	LDH	1155 U/L	N/A	281 U/L
	CEA	26.7 ng/mL	N/A	13.6 ng/mL
Diagnosis	Positive PAS	VATS biopsy at OSH	BAL	BAL
	FiO_2	100% (BiPAP)	95% (HFNC)	50% (ventilator)
	VV-ECMO cannulation	31F Avalon-RIJ	31F Avalon-RIJ	27F Avalon-RIJ
	Whole-lung lavage	18 L, right; 15 L, left	25 L, right; 20 L, left	21 L, right; 21 L, left
	Duration of cannulation (h)	48	24	48
	Extubation (h)	72	24	48
Postprocedure	Discharge (days)	8	3	6
	Cultures	*S. maltophilia*, MAC	Negative	MAC
	Repeat lavage	No	No	Yes, 6 months later
	GM-CSF therapy	Yes, inhaled	No	Yes, inhaled
	Spirometry (>3 months)	N/A	FVC 3.18 (58%); FEV1 2.63 (61%); FEV1/FVC 79%	FVC 3.83 (82%); FEV1 3.49 (93%); FEV1/FVC 81%
	Status (years post WLL)	Alive (5)	Alive (3)	Alive (3)
	Current symptoms	Mild	Mild	Asymptomatic

BAL indicates bronchoalveolar lavage; BiPAP, bilevel positive airway pressure; CEA, carcinoembryonic antigen; COPD, chronic obstructive pulmonary disease; CT, computed tomography; DM, diabetes; ED, emergency department; FEV1, forced expiratory volume in 1 second; FiO_2, fraction of inspired oxygen; FVC, functional vital capacity; GM-CSF, granulocyte-macrophage colony-stimulating factor; HFNC, high-flow nasal cannula; HTN, hypertension; LDH, lactate dehydrogenase; MAC, *Mycobacterium avium* complex; N/A, not available; OA, osteoarthritis; OSA, obstructive sleep apnea; OSH, outside hospital; PAS, periodic acid–Schiff; RIJ, right internal jugular; VATS, video-assisted thoracoscopic surgery; VV-ECMO, veno-venous extracorporeal membrane oxygenation; WLL, whole-lung lavage.

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